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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,601	01/26/2001	Myra A. Lipes	10276-015002	6880

26161 7590 07/01/2004

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/770,601	LIPES ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,30,31,60,61,64-74,79-83 and 86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 30, 31, 60, 61, 64-74, 79-83, and 86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed April 12, 2004 (hereinafter referred to as "the response") has been entered. Claims 27, 31, 64, 68, 70, 73, 74, and 82 have been amended. Claim 28 has been cancelled.

Accordingly, Claims 27, 30, 31, 60, 61, 64-74, 79-83, and 86 remain pending in the instant application.

The rejection of the claims under 35 U.S.C. 112, first paragraph, for lack of written description relating to various promoters that are active in IL cells is withdrawn in view of the claim amendments and the Declaration of Dr. Lipes.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 27, 30, 31, 60, 61, 64-73, 79-83, and 86 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediate lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous control region that includes the pro-opiomelanocortin (POMC) promoter, does not reasonably provide enablement for the use of cells having other genetic modifications and other promoters. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediate lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous promoter that directs expression of the nucleic acid in the intermediate lobe pituitary cell.

The specification discloses transgenic NOD mice that carry a transgene encoding proinsulin under the control of the POMC promoter. The transgenic intermediate lobe pituitaries were transplanted under the kidney capsule of spontaneously diabetic NOD mice. Transplantation resulted in significant weight gain and in the complete remission of diabetic symptoms (page 26, line 11). The grafts showed no evidence of lymphocytic infiltration. At page 26, lines 23-24, the specification discloses that the great majority of insulin secreted by the transgenic pituitaries is fully processed, mature insulin.

The specification fails to provide an enabling disclosure for the use of transgene constructs that do not encode insulin or do not include the POMC promoter because the proper regulation of insulin secretion is critical for successfully carrying out the claimed method. While the specification discusses a variety of strategies for providing glucose-stimulated insulin secretion (e.g. by further providing transgenes that encode glucokinase, ion channels that mediate glucose-stimulated insulin release, GLP-1, and/or GLUT-2) , specific guidance for actually achieving regulated insulin secretion is not provided to the skilled artisan. Achieving glucose-stimulated insulin secretion has been problematic in the art of *ex vivo* gene therapy and cell replacement therapy for diabetes. Halban et al. (2001) emphasize that the β-cell is remarkably sophisticated and that therapeutic strategies that use surrogate cells will have a number of hurdles to overcome to faithfully mimic the properties of this highly differentiated secretory cell (see abstract). The authors state that insulin is "normally secreted in a well-regulated fashion in rapid

response to the metabolic needs of the individual and most specifically (but not exclusively) to changes in circulating levels of glucose" (abstract). The reference discusses the numerous hurdles that have been encountered in the development of therapeutic strategies that rely on gene therapy or cell-replacement therapy. The authors conclude that "it will be essential to have well-regulated insulin secretion" (page 2189, column 2, paragraph 2) and that "[i]ntroducing glucose-sensitivity to otherwise insensitive cells may be more complex than previously imagined" (page 2189, column 2, paragraph 2).

Xu et al. (2003) discuss the challenges to coupling the synthesis and release of the transgene insulin to serum glucose concentrations. The authors state that "[u]nlike gene therapy for hemophilia ... diabetes gene therapy is much more complicated, as this involves not only insulin generation, but also its modification and release. Insulin is of vital importance in maintaining glucose homeostasis, and its unique role as the only anabolic peptide hormone necessitates strict regulation and fast-acting mechanisms to guarantee efficient insulin biosynthesis and secretion ... A major impediment to sucessful insulin gene therapy has been the difficulty in coupling the synthesis and release of the transgene insulin to serum glucose concentrations. This tight coupling between glucose stimulation and insulin secretion has become the objective of paramount importance to most researchers" (page 73, column 1, paragraph 2). The reference further emphasizes that the ideal surrogate cells would possess the came characteristics as the β cells including (i) glucose-dependent proinsulin gene transcription, (ii) proinsulin proteolytic processing, and (iii) glucose-dependent insulin secretion (page 71, column 1, paragraph 3).

Welsh (2000) provides a discussion of the prospects for gene therapy of diabetes mellitus that agrees with the analysis of Xu et al. (2003) and Halban et al. (2001) regarding the state of the art. Welsh points out that tight control of insulin release is essential to any therapeutic strategy. In discussing *ex vivo* gene therapy experiments and the various cell types used, Welsh states that

"[u]nfortunately none of these cells respond to glucose with physiological secretion of insulin. Instead, it is only possible to achieve regulation of insulin gene transcription by using promoter constructs that respond to glucose. Because transcription is a much slower process than regulated release from secretory granules, there is a substantial risk of the insulin production getting out of phase with fluctuations in glucose levels leading to episodes of severe hypoglycemia. Thus, the generation of a substitute β cell from non-β cells may prove to be exceedingly difficult" (page 181, column 1, paragraph 2).

Given the limited working examples and limited specific guidance for achieving regulated insulin secretion over the broad context of the claims, and further given the unpredictability in the art of *ex vivo* gene therapy for diabetes, one skilled in the art would have been required to engage in undue experimentation in order to practice the claimed method over the full scope.

At page 9 of the response, Applicants argue that IL cells have the proper prohormone processing machinery to produce and secrete fully processed, mature insulin sufficient to produce a therapeutic effect in a diabetic subject. The Declaration of Dr. Lipes argues that the instant rejection seems to be based on the erroneous belief that the POMC promoter is glucose-regulated. While it is evident that the POMC promoter is not glucose-regulated, the state of the art demonstrates that the level of insulin secreted must fall within the appropriate range to provide a therapeutic benefit. The production of sufficient and/or appropriate levels of gene product is one of the challenges facing *ex vivo* gene therapy. Thus, the success or failure of *ex vivo* gene therapy protocols often hinges, at least in part, on the use of appropriate regulatory regions that will provide enough gene product to be therapeutically beneficial. The cited art demonstrates that the use of appropriate regulatory regions, for gene therapy of diabetes, can reasonably be expected to be a key element in the success of any given protocol.

Thus, the rejection is maintained for reasons of record.

Allowable Subject Matter

Claim 74 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-0532.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER